UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Note to Reader
January 15, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

DATE: **October 8, 1997**

MEMORANDUM

SUBJECT: **METHIDATHION - *FQPA REQUIREMENT* -** Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland
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THROUGH: K. Clark Swentzel
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TO: Karen Whitby
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PC Code: 100301

BACKGROUND: On September 23, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Methidathion with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Methidathion as required by the Food Quality Protecting Act (FQPA) of 1996. The Committee's decisions are summarized below.

CC: Rick Whiting, Science Analysis Branch
Caswell File
LAN storage

A. INTRODUCTION

The Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Methidathion with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Methidathion as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document.

B. RESULTS

1. Neurotoxicity

In an acute delayed neurotoxicity study, no clinical or histopathological signs of neurotoxicity were seen in hens given single oral doses of Methidathion at 175 or 350 mg/kg (MRID No. 00011704). The Committee noted that the study did not assess for the potential of Methidathion to inhibit neurotoxic esterase (NTE) in hens.

In an acute neurotoxicity study, Sprague-Dawley rats were given an oral administration of Methidathion at 0, 1, 4, 8 or 15 mg/kg. For neurotoxicity, the NOEL was 4 mg/kg and he LOEL was 8 mg/kg based on decreased maze activity and differences in FOB parameters including tremors, bizzare behavior, abnormal gait, atxia, low arousal, decrease in forelimb grip strength, uncoordinated righting reflex. For cholinesterase inhibition, the NOEL was < 1 mg/kg (MRID Nos. 43145903 and 43590304).

In a subchronic neurotoxicity study, Sprague-Dawley rats were fed diets containing Methidathion at 0, 3, 10, 30 or 100 ppm (0.2, 0.6, 1.9, or 6.3 mg/kg/day in males and 0.2, 0.7, 2, or 7.2 mg/kg/day, in males and females, respectively) for 90 days. The NOEL was 3 ppm (0.2 mg/kg/day) and the LOEL was 10 ppm (0.6 mg/kg/day) based on statistically and biologically significant decreases in red blood cell, serum and brain cholinesterase activity (MRID No. 43582501).

2. Developmental Toxicity

The developmental toxicity studies in rats and rabbits showed no evidence of additional sensitivity of young rats or rabbits following pre- or postnatal exposure to Methidathion and comparable NOELs were established for adults and offspring.

In a developmental toxicity study pregnant Crl:CD(SD) BR rats received oral doses of Methidathion in 3% corn starch at 0, 0.25, 1.0, or 2.25 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 1.0 mg/kg/day and the LOEL was 2.25 mg/kg/day based on one death, decreases in body weight gain and food consumption, cholinergic signs indicative of cholinesterase inhition, exopthalmia, raspy respiration and vaginal bleeding. For developmental toxicity, the NOEL was 2.25 mg/kg/day (HDT); a LOEL was not established (MRID No. 40079807).

In a developmental toxicity study, pregnant New Zealand White rabbits were given oral doses of Methidathion at 0, 2, 6, or 12 mg/kg/ day during gestation day 7 through 19. For maternal toxicity, the NOEL was 6 mg/kg/day and the LOEL was 12 mg/kg/day based on clinical signs indicative of cholinergic activity. For developmental toxicity, the NOEL was 12 mg/kg/day (HDT); a LOEL was not established (MRID Nos. 40079809 and 40079810).

3. Reproductive Toxicity

In a one-generation reproduction study, Sprague-Dawley rats were fed diets containing Methidathion at 0, 5, 50, or 100 ppm (changed to 25 ppm at weaning of $F_{1a.}$ litters) for one generation. These doses were equivalent to 0,0.25, 2.5, or 5 (1.25) mg/kg/day. There was no increased sensitivity of pups over the adults. The parental/systemic NOEL was 5 ppm (0.25 mg/kg/day) and the LOEL was 50 ppm (2.5 mg/kg/day) based on tremors and decreased food consumption during lactation.. For reproductive toxicity, the NOEL was 5 ppm (0.25 mg/kg/day) and the LOEL was 50 ppm (2.5 mg/kg/day) based on decreased pup birth weight and pup weight during lactation.

In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing Methidathion at 0, 5, 25, or 50 ppm (0,0.25, 1.25, or 2.5 mg/kg/day) for two sucessive generations. There was no increased sensitivity of pups over the adults. The parental/systemic NOEL was 5 ppm (0.25 mg/kg/day) and the LOEL was 25 ppm (1.25 mg/kg/day) based on tremors and decreased food consumption during lactation and decreased ovarian weight. For reproductive toxicity, the NOEL was 5 ppm (0.25 mg/kg/day) and the LOEL was 25 ppm (1.25 mg/kg/day) based on decreased pup weight and an increased incidence of hypothermia with the appearance of starvation (MRID No. 40079811-13).

4. Cholinesterase Inhibition

Cholinesterase activity was not measured in the adults and offspring in the developmental toxicity studies or in the reproduction study. Therefore, no comparisons could be made for this endpoint between adults and offspring.

5. Developmental Neurotoxicity

There are sufficient data available to adequately assess the potential for toxicity to young animals following pre-and/or post-natal exposure to Methidathion. These include acceptable developmental toxicity studies in rats and rabbits as well as a 1 and 2-generation reproduction studies in rats. In addition, no treatment-related neuropathology was seen in studies conducted in hen or rats. Therefore, based upon a weight-of-the-evidence consideration of the data base, the Committee determined that a developmental neurotoxicity study in rats is not required.

6. Reference Dose (RfD)

An RfD of 0.0015 mg/kg/day was derived from the NOEL of 0.15 mg/kg/day and an Uncertainty Factor (UF) of 100. The LOEL was based on elevated hepatic enzymes, gross hepatic lesions, chronic hepatitis and inhibition of red blood cell cholinesterase actitivity at 1.33 mg/kg/day in dogs in a chronic toxicity study. The UF of 100 included a 10 for intra-species and 10 for inter-species variation.

7. Data Gaps

None.

C. CONCLUSIONS

The Committee's conclusions on the Uncertainty Factors for acute and chronic dietary risk assessments are as follows:

1. Acute Dietary Risk Assessment

The endpoint selected for acute dietary risk assessment is based on inhibition of plasma and red blood cell and brain cholinesterase activity at 0.6 mg/day in dogs. The NOEL was 0.2 mg/kg/day.

For acute dietary risk assessment, the Committee determined that an the **10 x** factor to account for enhanced sensitivity of infants and children (**as required by FQPA**) **should be removed**. **A Margin of Exposure of 100 is adequate** to ensure protection of this population from acute exposure to Methidathion for reasons stated below:

(i) No increased sensitivity of fetuses as compared to maternal animals following *in utero* exposure in developmental toxicity studies..

(ii) No increased sensitivity of pups as compared to adults in a multigeneration reproduction study.

(iii) No data gaps.

2. Chronic Dietary Risk Assessment

The endpoint for chronic dietary risk assessment is based on red blood cholinesterase

inhibition and hepatic toxicity observed at 1.33 mg/kg/day (LOEL) in dogs. The NOEL was 0.15 mg/kg/day. An UF of 100 applied to the NOEL; 10 X each for inter and intra species variability. Thus an RfD of 0.0015 mg/kg/day was derived.

For chronic dietary risk assessment, the Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children (**as required by FQPA**) **should be removed**. **The present UF of 100 is adequate** to ensure protection of this population from chronic exposure to Methidathion **Therefore, the RfD remains at 0.0015 mg/kg/day.** An UF of 100 is adequate since there was no indication of increased sensitivity to young animals following pre-and/or post-natal exposure to Methidathion as shown below:

(i) Developmental toxicity studies showed no increased sensitivity of fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.

(ii) Multi generation reproduction toxicity studies in rats showed no increased sensitivity of pups as compared to adults and offsprings.